Breast Cancer Res Treat (2007) 105:1–2
DOI 10.1007/s10549-007-9728-z

EDITORIAL

# Editorial

**Henning T. Mouridsen**



**Letrozole: 10 years and getting better**

Over the past decade, clinical trials have shown that aromatase inhibitors (AIs), as a class, are superior to tamoxifen in advanced and early hormone receptor-positive breast cancer. As a result of these trials, AIs have been approved in a variety of settings and are quickly replacing tamoxifen as standard adjuvant therapy for postmenopausal women with hormone-sensitive tumors. Of the three AIs currently approved, letrozole is the most potent inhibitor of aromatase activity and of tumor proliferation. This year marks the 10th anniversary of Novartis bringing letrozole to the market. Since then, letrozole has become one of a range of indispensable medications available to physicians for the treatment of early and advanced breast cancer.

This supplement will review the development of letrozole and its efficacy in several breast cancer treatment settings, as well as discuss the management of common comorbidities associated with the use of AIs.

The supplement will begin with "reminiscences from the early days," providing an historical overview of the letrozole development program by scientists involved in the discovery of letrozole in the laboratory, and the clinicians and statisticians who devised the structure of the trials. Modern third-generation AIs effectively block the production of estrogen without exerting effects on other steroidogenic pathways. Dr. Bhatnagar reviews the mechanism of action of letrozole, leading to greater suppression of estrogen than other AIs, including anastrozole, exemestane, formestane, and aminoglutethimide. He also discusses the series of uniquely designed letrozole clinical trials, which set the standard for the field and increased international exchange of ideas and expertise among investigators.

In the advanced breast cancer setting, letrozole is the only third-generation AI that has consistently demonstrated significant improvements in objective response rate, time to progression, and early overall survival. As the primary investigator of the PO25 study, I will describe the results of this trial, highlighting the evidence for the superiority of letrozole over tamoxifen as first-line endocrine therapy in postmenopausal women with advanced breast cancer.

The benefits of letrozole extend into the neoadjuvant setting as well. As neoadjuvant treatment, letrozole reduced tumor volume and allowed women with inoperable breast cancer or who were not candidates for breast-conserving surgery to undergo breast preservation procedures. Drs. Ellis and Ma discuss how letrozole, administered in the neoadjuvant setting, has also shown efficacy in the treatment of human epidermal growth factor receptor 2 (HER2)- and/or HER1-positive tumors.

Extended adjuvant letrozole is a new treatment paradigm that now offers women who have completed 5 years of tamoxifen the opportunity to further protect themselves against relapse. Letrozole was the first AI approved in the extended adjuvant setting. Dr. Goss summarizes the results from the pivotal NCIC MA.17 trial, which showed a significant reduction in recurrence risk, the risk of distant metastases, and a survival advantage in node-positive patients. The results from this landmark trial led to the approval of letrozole for this indication. Dr. Goss also discusses the results from the latest MA.17 analyses post unblinding, which demonstrate that letrozole is effective even in those women who have spent a prolonged period off tamoxifen. The benefit of letrozole continues with longer duration (at least out to 4 years), and the option of

H. T. Mouridsen (✉)
Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
e-mail: henning.mouridsen@rh.regionh.dk

extended adjuvant or late extended adjuvant therapy should be discussed with all patients completing adjuvant tamoxifen.

The results from the uniquely designed Breast International Group (BIG) 1-98 trial have led to the approval of letrozole as an initial adjuvant therapy. The eagerly awaited monotherapy arm analysis of the BIG 1-98 trial was recently presented in Istanbul at the 31st Annual European Society for Medical Oncology congress, and will be reviewed and compared with the primary core analysis by Drs. Koeberle and Thuerlimann. The monotherapy results have confirmed the findings from the primary core analysis, which showed that compared with tamoxifen, letrozole significantly reduced the risk of recurrence by 19% and especially reduced the risk of distant metastases by 27%. This is an extremely important finding, as the presence of distant metastases is often regarded as a marker of decreased survival, thus suggesting that the superior efficacy of letrozole in reducing the risk of distant metastases might also translate into a significant survival benefit. The benefit of letrozole extends to patients at increased risk of recurrence (i.e., node-positive and chemotherapy-treated patients), supporting the use of letrozole as standard adjuvant therapy for postmenopausal women with endocrine-responsive breast cancer.

The significance of the superior potency of letrozole compared to other AIs is often discussed. Dr. O'Shaughnessy will provide an insightful overview of the currently ongoing Femara versus Anastrozole Clinical Evaluation (FACE) trial, which is comparing the efficacy and safety of letrozole versus anastrozole in over 4000 hormone receptor-positive, node-positive postmenopausal patients. Node-positive patients were selected because this population has a higher risk of relapse, with events occurring earlier than in node-negative patients, thereby providing an answer more quickly than conducting a trial in a broader population including patients with node-negative tumors. Results of the FACE trial will provide important insights into the optimal adjuvant treatment strategy for hormone receptor-positive postmenopausal women with early breast cancer.

Although AIs have demonstrated superior efficacy and better overall safety compared with tamoxifen in randomized controlled trials, they do not provide the cardioprotective benefits associated with tamoxifen, and bone loss may be a concern with their long-term adjuvant use. However, the impact of these adverse events is difficult to assess because cardiovascular disease, bone loss, and osteoporosis commonly also occur in postmenopausal women not under treatment with AIs. Furthermore, most of the available safety data come from trials comparing AIs and tamoxifen, a drug with known cardioprotective and bone-sparing effects. As discussed by Dr. Perez, patients at a higher risk for osteoporosis can be managed using bone mineral density monitoring, and prophylactic bisphosphonates to protect long-term bone health. Importantly, AIs decrease the risks of thromboembolic and cerebrovascular events compared with tamoxifen, and the overall rate of cardiovascular events in patients treated with AIs is comparable to that recorded in placebo-treated patients and within the range seen in age-matched, non-breast cancer populations.

Of course, no discussion of therapy is complete without considering the patient's perspective. Thanks to the growing literature and access to the Internet, patient awareness of new adjuvant therapies has grown, and patients are now, in many cases, aware of their treatment options and what to expect in terms of efficacy and safety. Drs. Harbeck and Haidinger examine the clinical use of letrozole from the patient's perspective and assess how it has improved treatment outcomes across the breast cancer continuum, including advanced or metastatic breast cancer, extended and initial adjuvant and neoadjuvant therapy.

The supplement ends with a look into the future. A review by Drs. Ellis and Ma discusses the individualized use of letrozole treatment, tailored according to a patient's needs and in combination with other agents. This new treatment paradigm will greatly improve outcomes and has the potential to revolutionize breast cancer care.

I hope that this supplement will not only highlight the superior efficacy and safety profile of letrozole but will also further validate the use of AIs for the treatment of postmenopausal women with hormone-sensitive breast cancer.